

Remarks

Claims 1-9 and 11-34 were pending in the subject application. By this Amendment, claims 13, 17, 18, 22, 23, 26, 30, and 31 have been amended, claims 14 and 16 have been cancelled, and new claims 35 and 36 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 1-9, 11, 12, and 27-30 remain pending but withdrawn from consideration. Accordingly, claims 13, 15, 17-26, and 31-36 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants acknowledge that claims 1-9, 11, 12, and 27-30 have been withdrawn from further consideration as being drawn to a non-elected invention.

The claim amendments set forth herein have been done in order to lend greater clarity to the claimed subject matter and to expedite prosecution. The amendments and cancellation of the claims should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 13-18, 22, 23, and 26 have been rejected under 35 USC §112, second paragraph, as indefinite. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination.

The applicants appreciate the Examiner's careful review of the claims. Please note that the claims have been amended herein in accordance with the Examiner's helpful observations. For example, claims 13 and 26 have been amended to delete the optional step. Also, the term "suitable" has been removed from the claims. Furthermore, claims 13 and 26 have been amended to lend greater clarity to the claimed subject matter. With regard to claim 15, the applicants respectfully submit that, from the specification, it would be apparent to one skilled in the art that these sites can be used for removing the rescue allele. In any event, there is no ambiguity about what is covered by the claim. The applicants have also amended claims 17 and 18 to address the issues raised by the Examiner.

With regard to the legal test for meeting the requirements of 35 USC §112, second paragraph, the Court of Appeals for the Federal Circuit has stated:

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Miles Lab., Inc. v. Shandon, Inc.* 997 F.2d 870,875,27 USPQ2d 1123, 1126 (Fed. Cir. 1993) (internal citations omitted).

In view of the amendments set forth herein, the applicants respectfully submit that one skilled in the art would have no trouble understanding the metes and bounds of the claims and would be fully apprised of the scope of the claim. As stated by the CAFC, “§112 demands no more.”

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 112, second paragraph.

Claims 13, 14, 16, 20-22, 24, and 26 have been rejected under 35 USC §102(b) as being anticipated by Roemer *et al.* (WO 01/60975). The applicants respectfully traverse this ground for rejection because the Roemer *et al.* reference does not disclose each and every element of the applicants’ claimed method.

It is basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Cornell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

The Roemer *et al.* reference describes a method for creating a diploid mutant cell in which the dosage of a specific gene can be modulated. According to Roemer *et al.*, one allele of a target

gene is inactivated. This inactivation is achieved by producing a functional knock-out (a null mutant). The second allele is modified by having its promoter replaced by a regulated promoter of heterologous origin. Through this conditional promoter, the wildtype allele can be turned on to rescue the mutant phenotype of the cell, which is due to the null mutation. In contrast, rather than rescuing the cell by turning on expression of the wildtype gene, the present invention uses a cell in which the wildtype allele (referred to in the subject application as the “rescue” allele; see, for example, page 5, paragraphs 2 and 3 of the subject application) can be conditionally inactivated. In other words, rather than turning on the expression of the wildtype gene, the present invention switches off the expression of a wildtype gene in order to investigate the function of the mutated allele.

The cited reference does not disclose the use of a rescue allele that can be conditionally inactivated. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(b) based on the Roemer *et al.* reference.

Claims 13-17, 19-22, 24-26, and 34 have been rejected under 35 USC §102(b) as being anticipated by Shin *et al.* (*Nature*, 1999, 402:496-501). The applicants respectfully traverse this ground for rejection because the Shin *et al.* reference does not disclose each and every element of the applicants’ advantageous methods.

The method described by Shin *et al.* also comprises the conditional inactivation of a wildtype rescue allele using tet-responsive alleles of Ednrb according to Fig. 1 of Shin *et al.* In contrast to the subject application, Shin *et al.* does not teach a method that produces a mutated gene product that can interact with other components of the cell. This is due to the fact that the method of Shin *et al.* uses a replacement of a large genomic sequence part by a bacterial promoter (tTA or rTA). This interruption leads to a null-mutant that does not generate a mutated protein, as disclosed on page 498, left column, second paragraph, where it is stated that the expression of Ednrb^{tetO} was undetectable by northern analysis (with reference to Fig. 2A). Therefore, the present invention is not disclosed by Shin *et al.* Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(b) based on the Shin *et al.* reference.

Claims 13-22, 24-26, 32, and 34 have been rejected under 35 USC §103(a) as being obvious over Shin *et al.* and Gotthardt *et al.* (*J. Biol. Chem.*, 2003, 278(8):6059-6065). The applicants

respectfully traverse this ground for rejection because the cited references, taken either alone or in combination, do not teach or suggest the applicants' invention as presently claimed.

The shortcomings of the primary Shin *et al.* reference, as that reference relates to the current invention, have been discussed in detail above. The Gotthardt *et al.* reference does not cure, or even address these shortcomings.

It is well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ____ (2007). Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." *Id.*

In the current case, there would be no reason (or expectation of success) to combine the cited references to arrive at the current invention. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103 based on Shin *et al.* in view of Gotthardt *et al.*

Claims 13-17, 19-25, and 34 have been rejected under 35 USC §103(a) as being obvious over Roh *et al.* (*Mol. Endocrinol.*, 2001, 15(4):600-613) and Tian *et al.* (*Developmental Biology*, 2002, 242:204-223). In addition, claims 13, 18, 26, and 32 have been rejected under 35 USC §103(a) as being obvious over Roh *et al.* and Tian *et al.*, and further in view of Gotthardt *et al.* The applicants respectfully traverse these grounds for rejection because the cited references, taken either alone or in combination, do not teach or suggest the applicants' invention as presently claimed.

In accordance with the present invention, a mutated protein is produced in a cell together with a wildtype protein that can be conditionally switched off in the cell. Advantageously, this system provides a convenient means of studying a myriad of mutations in parallel, in particular, point mutations of one allele, in an easy and efficient fashion. It is, for example, possible to produce several embryonic stem cells (ES) each containing a rescue (wildtype) allele of a certain gene that can be conditionally inactivated, and a mutated allele of the same gene, such that each ES cell expresses a different mutated protein. After the conditional inactivation of the rescue allele, for example, by excising the allele using the lox/cre system, the cell then only expresses the particular

point mutant. Thereby, each ES expresses a different point mutant. This allows for an efficient means of analyzing the function of a particular gene or a particular domain or even amino acid of a protein *in vivo*, without impeding the growth of the cell prior to the conditional inactivation of the rescue allele.

As noted above, the mere fact that the purported prior art could have been modified or applied in some manner to yield applicant's invention does not make the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125,1127 (Fed. Cir. 1984). An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Spinnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

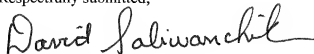
In this case, the cited references do not disclose or suggest the advantageous methods claimed by the current applicants. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103 based on Roh *et al.* and Tian *et al.* (claims 13-17, 19-25, and 34), and further in view of Gotthardt *et al.* (claims 13, 18, 26, and 32).

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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